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Navigating Treatment Goals With a CDK4/6 Inhibitor in HR+/HER2- mBC

Announcer:

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This medical industry feature, titled "Navigating Treatment Goals With a CDK4/6 Inhibitor in HR+/HER2- Metastatic Breast Cancer," is sponsored by Novartis Pharmaceuticals Corporation, which participated in the review of this content. This program is intended for US health care professionals.

The speakers have been compensated by Novartis Pharmaceuticals Corporation to conduct this presentation.

Dr Turck:

This is ReachMD and I'm your host, Dr Charles Turck. Are you aware of the data that are shifting health care providers' first-line choice of cyclin-dependent kinase 4 and 6, or CDK4/6 inhibitor, for hormone receptor-positive and human epidermal growth factor receptor 2-negative, or HR+/HER2-, in metastatic breast cancer patients?

Welcome to the first podcast in a series of 3, where we will discuss and share clinical perspectives on KISQALI, which has the generic name ribociclib, starting with overall survival. KISQALI is a CDK4/6 inhibitor indicated for the treatment of adults with HR+/HER2- metastatic breast cancer. It's approved for use in combination with an aromatase inhibitor as initial endocrine-based therapy, or fulvestrant as initial endocrine-based therapy, or following disease progression on endocrine therapy in postmenopausal women or in men.

Joining me to discuss the MONALEESA-2 study and findings is Dr Naomi Dempsey, MD. Dr Dempsey, thanks for being here today.

Dr Dempsey:

Thank you for having me.

Dr Turck:

To get us started, Dr Dempsey, let's begin with some background on the MONALEESA-2 study. Can you tell us about its design and objectives?

Dr Dempsey:

Absolutely. I'm excited to talk about the MONALEESA-2 trial. We know that overall survival is the number one treatment goal for the majority of patients with metastatic breast cancer, and this trial definitely addresses that. MONALEESA-2 was a randomized, double-blind, placebo-controlled phase 3 study of KISQALI plus letrozole versus placebo plus letrozole for the treatment of postmenopausal patients with HR+/HER2- metastatic breast cancer who received no prior therapy for advanced disease. The study looked at progression-free survival as the primary end point, and overall survival as a secondary end point.

It was designed to evaluate the efficacy and safety of KISQALI in combination with letrozole, versus letrozole alone, for the first-line treatment of postmenopausal patients with HR+/HER2- metastatic breast cancer.

Dr Turck:

And could you elaborate on the significance of overall survival in your practice when selecting a CDK4/6 inhibitor?

Dr Dempsey:

Of course. Prolonging life is the foremost priority for patients with metastatic breast cancer during their treatment journey, and for good reason. Naturally, patients want to maximize their time with loved ones and time for their personal goals. Extending overall survival allows them to accomplish exactly that. Considering these factors, it's clear that overall survival is paramount for patients with metastatic breast cancer, along with being the most reliable end point in pharmacotherapy. By keeping this goal in mind, I can be confident that I'm delivering care that best aligns with patients' needs.

Dr Turck:

For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and today I'm speaking with Dr Naomi Dempsey to discuss the MONALEESA-2 trial, which evaluated the efficacy and safety of KISQALI plus letrozole as the first-line treatment of postmenopausal HR+/HER2- metastatic breast cancer patients.

Now, let's dig into the data. In the MONALEESA-2 trial, patients receiving KISQALI plus letrozole experienced over 5 years median overall survival. What was your reaction to this data and what implications did it have for your practice?

Dr Dempsey:

So, at a median follow-up of 80 months, the median overall survival was 63.9 months for the KISQALI plus letrozole group compared to 51.4 months for the placebo plus letrozole group. This translates to an over 1-year increase in median overall survival. Additionally, at 6 years, the survival rate of patients receiving KISQALI plus letrozole was 44% versus 32% with placebo plus letrozole, showing that overall survival benefit increased over time. The MONALEESA-2 trial paves a way to establishing an avenue of care for postmenopausal patients with HR+/HER2- metastatic breast cancer. The trial demonstrated an impressive increase in median overall survival compared with letrozole alone, providing robust evidence for us as clinicians to seriously consider this combination therapy as a valuable first-line treatment.

Dr Turck:

Wonderful. And before we end this conversation, Dr Dempsey, I'd like to get your thoughts on the National Comprehensive Cancer Network, or NCCN, recognizing KISQALI as a Category 1 Preferred first-line treatment option in combination with an aromatase inhibitor for patients with HR+/HER2- metastatic breast cancer. What are your key takeaways on this designation?

Dr Dempsey:

Well, the NCCN has recognized KISQALI as the only Category 1 Preferred first-line treatment option in combination with an AI for patients with HR+/HER2- metastatic breast cancer. From a health care provider standpoint, NCCN Guidelines really help in the decision-making process for those involved in oncology care, and ensures that we are aligned on one goal, which is the improvement of patient care and outcomes. In addition, this designation further reflects the robust evidence that KISQALI offers, as well as the growing body of key opinion leaders who endorse it. Furthermore, the MONALEESA-2 findings we just discussed make KISQALI a valuable option for the first-line management of HR+/HER2- metastatic breast cancer, and ultimately contributes to improving patient outcomes.

Dr Turck:

That's a wonderful way to round out our discussion. I want to thank my guest, Dr Naomi Dempsey, for sharing insights on KISQALI and the MONALEESA-2 data. Dr Dempsey, it was great speaking with you today.

Dr Dempsey:

Thank you. I'm happy to help, and I enjoyed this conversation.

Dr Turck:

And before we close, let's take a moment to review some Important Safety Information.

Announcer:

Indications

KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women

or in men.

IMPORTANT SAFETY INFORMATION

Interstitial lung disease/pneumonitis. Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

Across clinical trials in patients with advanced or metastatic breast cancer treated with KISQALI in combination with an aromatase inhibitor or fulvestrant ("KISQALI treatment groups"), 1.6% of patients treated with KISQALI had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis.

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI.

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These electrocardiogram (ECG) changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the non-steroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Hepatobiliary toxicity. Across KISQALI treatment groups, increases in transaminases were observed. Across all trials, grade 3/4 increases in alanine aminotransferase (ALT) (11% vs 2.1%) and aspartate aminotransferase (AST) (8% vs 2%) were reported in the

KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days and median time to resolution to grade ≤2 was 21 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the upper limit of normal (ULN) and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

Neutropenia. Across KISQALI treatment groups neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 17 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1.7% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 1%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. Most common (incidence ≥20%) adverse reactions include infections, nausea, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, and back pain.

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased.**

Please see full Prescribing Information on this site or on **www.kisqali-hcp.com**.

Announcer:

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